**Introduction to Endocrine Disorders**

- **Hormones**
  - Self-regulating system (homeostasis)
  - Affect:
    - Growth
    - Metabolism
    - Reproduction
    - Fluid and electrolyte balance

**Hormone actions**

- Peptide hormone: GH, PRL, oxytocin etc.
- Steroid hormone, Thyroid hormone, cortisol etc.

**Modulation of hormone levels**

- **Hormone synthesis**
  - Many steps
  - Required enzymes
- **Hormone release**
- **Regulation of hormone production**

**Endocrine gland**

- Hormone synthesis
- Hormone structure
- Hormone transportation
- Receptor
- Hormone synthesis
- Hormone structure
- Receptor
- Postreceptor

- **Blood stream**
- **Target tissue (gland)**
- **Blood stream**
- **Target tissues**

- **Hormone release**
  - Constant (thyroid axis)
  - Episodic
    - On demand (after a meal; during stress)
      - Insulin; ACTH
Diurnal (many hormones)

- Light entrained (ACTH/cortisol)
- Sleep entrained (GH, testosterone)

Pulsatile (most hormones)

 Regulation of hormone production

Negative feedback

- Important aspect of hormone regulation
- May be exerted by another hormone
  - Testosterone inhibits LH
  - Thyroxin inhibits TSH
- May be exerted by a nonhumoral signal
  - Calcium inhibits PTH
  - Glucose inhibits glucagon

Negative feedback

- Lack of appropriate negative feedback response provides clues to the pathophysiology
  - Causes of low thyroid hormone?
    - Pituitary problem; inadequate TSH
    - Thyroid problem; can't make adequate throxine
    - How do you differentiate?
Negative feedback

- Lack of appropriate negative feedback response provides clues to the pathophysiology
  - Causes of low thyroid hormone?
    - Pituitary problem; ie inadequate TSH
    - Thyroid problem; can't make adequate thyroxine
  - How do you differentiate?
    - Measure both TSH and thyroxine
    - If TSH is not elevated (inappropriate negative feedback response), conclude pituitary defect

Disorders of the endocrine system

- Hormone Deficit
- Hormone Excess
- Hormone Resistance (Insensitivity)

Examples

- Type I diabetes
- Addison's disease
- Panhypopituitarism
- Polyglandular failure
- Hypothyroidism

Hormone Transport

- Circulating H
  - Free H
  - Bound H
- Free hormone
  - Active
  - Correlated with inhibition, clinical states of hormone excess or deficiency
- Bound hormone
  - Inactive
  - Reservoir

Hormone Deficit

1. Glandular Destruction
   - Autoimmune disease
   - Infection
   - Neoplasms
   - Hemorrhage

2. Extraglandular Disorders
   - Neoplasms, ischemic, infection
   - Autoimmune disease
   - Organ produce hormone
     - Kidney, liver, heart etc.
   - Convert hormone precursor to active form
     - Kidney
   - Hormone degradation or sensitivity
Examples
Renal diseases can result in
- Hypoaldosteronism
  renin-angiotensin aldosterone system
- Anemia
  erythropoietin
- Abnormal calcium and phosphate balance
  $1_a$-hydroxylase

Hormone degradation or sensitivity
Glucocorticoid Rx ➔ Insulin sensitivity
Anticonvulsant drug ➔ Cortisol metabolism

Hormone Excess
- Neoplasms
  Hormone-producing tumor
    - Pituitary gland
    - Thyroid gland
    - Adrenal gland etc
- Autoimmune disease
  - Hyperthyroidism: Ab similar to TSH
  - Autoimmune disorder leading to endocrine hyperfunction is rare
- Exogenous hormone

3. Defects in Hormone Biosynthesis
Defects in gene which
- Encodes hormone
- Regulates hormone production
- Encodes hormone-producing enzyme

Examples
GH Deficiency
Mutation in Pit-1 gene
Mutation in GH gene
Mutation in GHRH gene
Dwarfism
Abnormal Biosynthesis of Adrenal Gland Hormones ➔ Congenital Adrenal Hyperplasia
21-hydroxylase def
11 $\beta$-hydroxylase def

Syndromes of hormone excess due to Administration of exogenous hormone
- Cushing’s syndrome from exogenous glucocorticoids Rx
e.g. autoimmune disease - nephrotic syndrome, SLE etc
- Infertility in some athletes from exogenous androgen
to improve physical performance
  (diminish pulsatile release)
**Defect in Hormone Sensitivity**

**A. Genetic Defect**
- Genetic defect in receptors
  - glucocorticoids, Thyroid H, androgens, vitamin D, leptin etc
- Absent, does not bind to its ligand
- can cause overproduction of other hormones

**Example**

- Glucocorticoid receptor defect → ↑ACTH
- Mineralocorticoid level

**B. Acquire Defect**
- Target tissue damage and loss ability to response to hormone

**Examples**
- Renal disease
  - Insensitivity to vasopressin
- Liver disease
  - Insensitivity to glucagon

**Post-receptor defect**

- Type 2 DM
  - Abnormal in signaling transduction

➢ May occur from hormone therapy

- Hormone replacement → ↓Hormone receptor
  - “Down regulation”

- GnRH replacement → ↓GnRH receptor
  - Androgen production ↓
  - Or
  - Prostate cancer Rx (anti-androgen) → ↓Androgen production
Some Useful Laboratory Investigations in Endocrine Disorders

- Hormone measurement
  - Direct measurement of hormone level
    - Immunoassays: RIA, ELISA
    - Nonimmunologic assay: Chemical assays

- Indirect measurement of hormone level
  - Stimulation test
  - Suppression test

- Receptor assays
  - Example: Breast cancer

- Diagnosis of genetic disorder
  - PCR
  - RFLP
  - Examples: MODY, Breast cancer

Vitamin D Synthesis

- Skin
  - 7-Dehydrocholesterol
  - Vitamin D

- Liver
  - 25(OH)Vitamin D

- Kidney
  - 1α-Hydroxylase
  - 1,25-Dihydroxyvitamin D (Active metabolite)
  - Tissue-specific Vitamin D responses

Adrenal steroids biosynthesis

- Z. Glomerulosa
  - Mineralocorticoid pathway

- Z. fasciculata
  - Glucocorticoid pathway

- Z. rutilis
  - Androgen pathway

- Cholesterol
  - 17α-Hydroxyprogrenolone
  - Dihydroepiandrosterone

- Progesterone
  - 17α-Hydroxyprogrenolone

- 11-Deoxycorticosterone
  - Corticosterone
  - Alloxasterone

- Androgens
  - Testosterone
  - Estradiol